REMARKS

Upon entry of these amendments, claims 1-13, 15-17, and 20-21 will be pending in this application. Claims 14, 18, and 19 have been cancelled herein, without prejudice or disclaimer. Claim 1 has been amended herein to more precisely define the claimed invention. Specifically, claim 1 has been amended to specify that the glutamate antagonist is administered directly into herniated disc tissue. Support for this amendments can be found at least page 2, lines 10-11 and page 14, lines 18-20 of the as-filed specification. Claim 21 has been amended herein to correct a typographical error.

Accordingly, no new matter has been added herein.

Claim Rejections--35 U.S.C.§ 103

Claims 1-7, 12-17, and 19-21 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Harrington et al., Spine 25(9):929-36 (2000) ("Harrington et al.") in view of Lawand, et al., Euro J of Pharmacology 324:169-77 (1997) ("Lawand et al."). According to the Examiner, "Harrington et al. teaches that disc radiculopathy can be treated with epidural glutamate receptor antagonists." (Office Action at page 3). Although the Examiner concedes that Harrington et al. does not teach the administration of a glutamate antagonist directly into herniated disc tissue, the Examiner concludes that "it would have been obvious to one of ordinary skill in the art at the time of the invention to administer glutamate antagonist directly to said herniated disc tissue." (Office Action at page 3). Moreover, while the Examiner also concedes that Harrington et al. does not teach an ionotropic glutamate receptor or NMDA type receptor in a method to alleviate pain, the Examiner relies on Lawand et al., which "teaches the intra-articular injection in knee joint of either an NMDA or a non-NMDA glutamate receptor (CNQX) attenuated the thermal hyperalgesia and the mechanical allodynia produced by glutamate, arginine, and aspartate . . ." (Office Action at page 4). Thus, the Examiner concludes that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to administer iontropc glutamate receptor or NMDA type receptor antagonists in a method to alleviate pain in [a] mammal. The motivation to do so is taught by Harrington and Lawland [*sic.*] et al." (Office Action at page 4). Applicant traverses.

As an initial matter, Applicant notes that claims 14 and 19 have been cancelled herein, without prejudice or disclaimer. Thus, this rejection, as it applies to these claims, is moot and should be withdrawn.

Moreover, as noted, claim 1 has been amended herein to specify that the glutamate receptor antagonist is administered directly into herniated disc tissue. Harrington et al. (either alone or in combination with Lawand et al.) does not teach or suggest such a method.

Specifically, as acknowledged by the Examiner, Harrington et al. does not teach the administration of the glutamate antagonist directly into herniated disc tissue. (*See* Office Action at page 3). Rather, Harrington et al. discloses the treatment of disc radiculopathy via epidural administration of glutamate receptor antagonists. (*See* Harrington et al., Abstract).

With respect to administration directly into herniated disc tissue, the environment of the disc space is not in direct communication with the epidural space. In fact, as shown in Table 1 of Adams, et al., J. Bone Joint Surg. Br. 68:36-41 (1986) (courtesy copy enclosed), only in cases of severe disc degeneration (*e.g.*, grade 5 rupture) is there any communication whatsoever between the disc and the epidural space. As such, Applicant submits that one skilled in the art would also not have been motivated to apply the method described in Harrington et al. to the claimed method of administering the glutamate antagonist directly into herniated disc tissue. Likewise, in view of the anatomical differences and physical separation between the disc tissue and the epidural space, the ordinarily skilled artisan would similarly not have had a reasonable expectation of success in adapting the Harrington et al. method to that of claim 1.

Thus, for all of these reasons, Applicant submits that claim 1, as amended herein, is not obvious in view of Harrington et al.

With regard to elbow joints, Applicant submits that the teaching of Harrington et al. would not have motivated one of ordinary skill in the art to administer the glutamate receptor antagonist into an elbow joint, as recited in claim 17. Elbows are significantly different in structure and function from the epidural space of the spinal column. Those skilled in the relevant art will recognize that a joint is an area where two bones are attached for the purpose of motion of body parts (*see* definition from www.medicinenet.com (courtesy copy enclosed), whereas the epidural space is a fat-filled space external to the dura matter ensheathing the spinal cord (*see* definition www.medilexicon.com (courtesy copy enclosed)). Thus, because of these anatomical differences, one skilled in the art, by virtue of the teaching of Harrington et al., would not have

been motivated to adapt the methods described in Harrington et al. (*i.e.*, administration to the epidural space) to an elbow joint (nor would they have had a reasonable expectation of success in doing so).

Therefore, Applicant submits that claim 17 is also not obvious in view of Harrington et al.

The addition of Lawand et al. does not cure these deficiencies in the teachings of Harrington et al. Specifically, Lawand et al. describes the role of excitatory amino acid receptor involvement in peripheral nociceptive transmission. Lawand et al. injected combinations of excitatory amino acids into the knee joints of rats in order to induce the development of hyperalgesia and allodynia. Subsequent intra-articular injection of NMDA or non-NMDA glutamate receptor antagonists was able to attenuate these symptoms of hyperalgesia and allodynia. (*See* Lawand et al., Abstract). However, there is no teaching or suggestion in Lawand et al. of the administration of a glutamate receptor antagonist into an elbow joint space or into herniated disc tissue in order to inhibit the binding of free glutamate liberated from degenerating cartilage tissue to glutamate receptors in order to alleviate pain. Moreover, Lawand et al. also observed that the administration of individual excitatory amino acids failed to produce symptoms of heat hyperalgesia or mechanical allodynia. (*See* Lawand et al. at page 174, 1st column).

Therefore, contrary to the Examiner's contention, the combination of Harrington et al. and Lawand et al. does not teach or suggest all of the limitations of the invention recited in claims 1 (as amended herein) and 17. Thus, the ordinarily skilled artisan would not have combined the teachings of these references in order to develop the claimed methods of alleviating pain associated with degenerating cartilage. As such, Applicant submits that claims 1 and 17 are not obvious in view of these references. Accordingly, this rejection should be withdrawn.

Moreover, dependent claims 2-7, 12-13, 15-16, and 20-21 each depend (directly or indirectly) from amended claim 1. As such, they necessarily contain all of the limitations of that claim. Therefore, for the reasons articulated above, Applicant submits that these dependent claims are also non-obvious over Harrington et al. in view of Lawand et al. Thus, this rejection of these claims should also be withdrawn.

Claim 18 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Harrington et al. in view of Lawand et al. as applied to claims 1-7, 12-17, and 19-21, and in view of Takahashi et al., Pain 75:391-94 (1998) ("Takahashi et al.").

Claim 18 has been cancelled herein, without prejudice or disclaimer. Thus, this rejection is moot and should be withdrawn.

Claims 1, 8, and 11 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Harrington et al. (as applied to claims 1-7, 12-17, and 19-21) and in view of Stanfa et al., Neuroscience 93(4):1391-98 (1999) ("Stanfa et al."). According to the Examiner, it would have been obvious to one skilled in the art to use the KA receptor antagonists described in Stanfa et al. in a method of treatment to alleviate pain. (*See* Office Action at page 7). The Examiner further notes that "[t]he motivation to do [so] is provided by Harrington et al. and Stanfa et al." (Office Action at page 7). Applicant traverses.

As described above, amended claim 1 is not obvious in view of Harrington et al. Moreover, because claims 8 and 11 depend (directly or indirectly) from amended claim 1, these claims necessarily contain all of the limitations of that claim. Therefore, these claims are also not obvious in view of Harrington et al., for the reasons set forth above.

The addition of Stanfa et al. does not cure the deficiencies in the teachings of Harrington et al., as Stanfa et al. does not describe or suggest a method for inhibiting free glutamate released from degenerating cartilage tissue from binding to glutamate receptors on a neuronal cell of a cartilaginous tissue. Rather, Stanfa et al. examined a non-NMDA receptor antagonist (NBQX) as well as a KA receptor antagonist (LY382884) in order to examine the role of non-NMDA receptors in the spinal transmission of nociception in normal animals as well as animals with carrageenan inflammation. In fact, Stanfa et al describes the intrathecal and/or spinal administration of these compounds. (*See, e.g.*, p. 1392, 2nd col., p. 1394, 1st col., p. 1394, 2d col.). However, nothing in Stanfa et al. teaches or suggests the desirability of administering these glutamate antagonists into joint space of an articulating joint or directly into herniated disc tissue.

Thus, for all of these reasons, Applicant submits that claims 1, 8, and 11 are not obvious over Harrington et al., either alone or in combination with Stanfa et al. Therefore, this rejection should be withdrawn.

Finally, claims 1, 9, and 10 have been rejected under 35 U.S.C. § 113(a) as unpatentable over Harrington et al. (as applied to claims 1-7, 12-17, and 19-21) in view of Garrett, Biol. Res. For Nursing, 1(4):310-20 (2000) ("Garrett"). According to the Examiner, while Harrington et al. does not teach a method of alleviating pain by administering metabotropic glutamate receptor antagonists, "Garrett teaches that L-AP3 a metabotropic glutamate receptor antagonist exhibited an antinociceptive effect in animals linking effective treatment of hyperalgesia with [a] metabotropic glutamate receptor". (Office Action at p. 7). Thus, the Examiner concludes that the teachings of Harrington et al. and Garrett provide the motivation for the ordinarily skilled artisan to use metabotropic glutamate receptor antagonists to alleviate pain. (*See* Office Action at p. 7). Applicant traverses.

As noted above, claim 1, as amended herein, is not obvious in view of Harrington et al. As claims 9 and 10 each depend from claim 1, they necessarily contain all of the limitations of that claim. Thus, Applicant contends that these claims are similarly not obvious in view of Harrington et al.

The addition of Garrett fails to remedy the deficiencies in Harrington et al. that are articulated above. Specifically, while Garrett reviews the role of the metabotropic glutamate receptor 1A in pain transmission and central sensitization and indicates that L-AP3 exhibited an antinociceptive effect in animals, thereby linking effective treatment of hyperalgesia with this receptor (*see* Garrett at p. 316,2nd col.), Garrett does not describe or suggest the use of glutamate antagonists to block the binding of free glutamate released from degenerating cartilage. In addition, Garrett also does not describe or suggest the administration of such antagonists into the joint space of articulating or directly into herniated disc tissue.

Thus, because Harrington et al. (either alone or in combination with Garrett) does not teach or suggest all of the limitations of claim 1, as amended herein (and, thus, of claims 9 and 10), Applicant submits that these claims are not obvious in view of these references. Therefore, this rejection has been overcome and should be withdrawn.

CONCLUSION

Applicant submits that this paper is fully responsive and that the application is in condition for allowance. Such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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